ORIGINAL ARTICLE

# Herpes Zoster Recurrences More Frequent Than Previously Reported

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OBJECTIVE: **To present population-based estimates of herpes zoster (HZ) recurrence rates among adults.**

PATIENTS AND METHODS: **To identify recurrent cases of HZ, we reviewed the medical records (through December 31, 2007) of all Olmsted County, Minnesota, residents aged 22 years or older who had an incident case of HZ between January 1, 1996, and December 31, 2001. Kaplan-Meier curves and Cox regression models were used to describe recurrences by age, immune status, and presence of prolonged pain at the time of the incident HZ episode.**

RESULTS: **Of the 1669 persons with a medically documented episode of HZ, 95 had 105 recurrences (8 persons with >1 recurrence) by December 31, 2007, an average follow-up of 7.3 years. The Kaplan-Meier estimate of the recurrence rate at 8 years was 6.2%. With a maximum follow-up of 12 years, the time between HZ episodes in the same person varied from 96 days to 10 years. Recurrences were significantly more likely in persons with zoster-associated pain of 30 days or longer at the initial episode (hazard ratio, 2.80; 95% confidence interval, 1.84-4.27; *P*<.001) and in immunocompromised individuals (hazard ratio, 2.35; 95% confidence interval, 1.35-4.08; *P*=.006). Women and anyone aged 50 years or older at the index episode also had a greater likelihood of recurrence.**

CONCLUSION: **Rates of HZ recurrence appear to be comparable to rates of first HZ occurrence in immunocompetent individuals, suggesting that recurrence is sufficiently common to warrant investigation of vaccine prevention in this group.**

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**CI = confidence interval; HZ = herpes zoster**

Herpes zoster (HZ), or shingles, is usually considered a once-in-a-lifetime experience, with HZ recurrences thought to be limited to immunocompromised individuals. The plausibility, actual occurrence, and frequency of recurrent HZ have been debated.[1-5] Studies of HZ recurrence often focus on special populations with hematologic malignancies or exposure to chemotherapeutic or immunotoxic agents like arsenic,[6-9] or they are population studies with small numbers of cases or short follow-up periods.[10-16]

This study assessed the rate of HZ recurrence with up to 12 years of follow-up in a population-based cohort of 1669 persons with a confirmed previous episode of HZ between January 1, 1996, and December 31, 2001. Like the index episodes, HZ recurrences were required to meet predefined diagnostic criteria of dermatomal rash and pain.[17-20] These data should provide health care professionals, insurers, and policy makers a more robust basis for practice, insurance, and policy decisions regarding prevention and treatment of HZ recurrences.[21]

## PATIENTS AND METHODS

We reviewed the medical records of a community population–based cohort of people with a confirmed episode of HZ followed up for recurrence for as long as 12 years after the index episode. Recurrence rates were expressed by time from the index episode to the first recurrence and stratified by sex, age, and immune status (immunocompromised or immunocompetent) as assessed at the time of the initial or index episode of HZ. Data from the Rochester Epidemiology Project[22,23] made it possible to identify all care provided to each of these individuals by any outpatient or inpatient health care facility within the county during the follow-up period.

Identification and confirmation of the index episodes of HZ have been described previously.[17] Briefly summarized, the original incidence study looked at the medical records of all residents of Olmsted County, Minnesota, aged 22 years or older who, according to administrative data, presented to any health care site with an acute HZ episode between January 1, 1996, and December 31, 2001. Using detailed medical record review, we confirmed the index HZ case and collected data on HZ complications, treatment, and immune status. Any person with an administrative HZ code before the period of interest (January 1, 1996, through December 31, 2001) was excluded from the cohort in an effort to assess rates of first HZ occurrence.

For this recurrence study, the medical records of all individuals with a confirmed HZ episode in the initial incidence study were reviewed from the date of their index HZ episode through December 31, 2007 (ie, a 6- to 12-year follow-up) to identify HZ recurrences. All medical records of all Olmsted County, Minnesota, health care facilities were reviewed to identify any recurrences for each individual in

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the cohort. More than 98% of all care of Olmsted County, Minnesota, residents is provided within the county, thereby assuring that our review would identify essentially all of the medically attended HZ recurrences.[22]

The diagnostic requirements for confirmation of an HZ recurrence were the same as for the index episode: cases had to be seen by a physician or other clinician, with documentation of a characteristic vesicular rash accompanied by pain or dysesthesia in a dermatomal pattern, unless the HZ was specifically diagnosed as "disseminated." The specificity of these clinical characteristics for the diagnoses of HZ are reported to be between 87.0% and 98.8%, confirming the validity of a clinical rather than laboratory diagnosis of HZ.[18-20] Review of the medical records for administrative codes suggesting HZ recurrences led to the exclusion of 23 cases because HZ was only one of a number of possible diagnoses listed as the cause of new-onset pain. To be considered an actual recurrence required subsequent notation of a typical rash and pain diagnosed as HZ, or a positive HZ virus culture or positive findings on polymerase chain reaction, if ordered. The site of the recurrence was recorded using the same anatomic coding system as used in the incidence study, making it possible to determine if the recurrence was at the same or a different site as the index episode.[17] To be considered to have occurred at different sites, the index and recurrent HZ episodes had to be in a different region of the body (eg, face and trunk, or leg and trunk) because adjacent dermatomes within the trunk might be difficult to distinguish clinically.

No possible HZ recurrent episode was counted as a recurrence if it occurred less than 3 months after the initial HZ episode was diagnosed. This was done to address concerns of relapse or slow healing of the index HZ episode in elderly patients. For any cases that occurred between 90 and 180 days, medical record review was used to confirm that the rash was different from the initial episode and that the recurrence did not appear from medical record data to be a continuation of the initial case. Doing so was especially important in cases that had eye involvement, the complications of which can be permanent (eg, loss of vision).

The same nurse abstractors who collected the data for the HZ incidence study also collected the data on recurrences using similar data collection tools and the same data definitions and dictionaries. As in the incidence study,[17] procedures included testing of interrater reliability[24] and weekly team meetings to review any complex cases. All final determinations were made by the lead clinical investigator (B.P.Y.).

### Statistical Analyses

Results were summarized using simple univariate statistics. Cumulative recurrence rates were plotted using Kaplan-Meier curves. Recurrence rates by time from index HZ episode to first recurrence were estimated using Kaplan-Meier statistics, with individuals censored at the time of dying or moving from the community. Risk factors were tested for association using Cox proportional hazards regression. Reported *P* values and confidence intervals (CIs) are from likelihood ratio tests in univariate models and from Wald tests for joint models. Cox models were evaluated using methods of Grambsch and Therneau (1994).[25] Cox regression was also used to examine trends in recurrence rates by age and sex. Rates of contralateral recurrence were compared using the McNemar test.

We used comparison of expected to observed rates of HZ cases to assess the comparability of the calculated HZ recurrence rates with our age- and sex-specific HZ incidence rates.[17] The expected number of new HZ episodes that would occur in 8 years of follow-up was estimated on the basis of age-specific HZ incidence rates in the cohort of 1669 persons with a confirmed index HZ episode, using their specific age and sex distribution. Because the rate of HZ increased with age, each index participant was classified in his/her initial age- and sex-specific incidence rate category, with age increased incrementally by 1 year for each of the years in the 8-year follow-up period. The expected number of HZ cases was compared to the observed number of recurrences using a 2-sample Poisson F-test, allowing us to statistically compare rates of incidence and recurrence in a community population.

## RESULTS

Of the 1669 adults with an index episode of HZ between January 1, 1996, and December 31, 2001, 1005 (60.2%) were women and 139 (8.3%) were immunocompromised at the time of the index HZ episode; median age was 59.4 years (mean, 59.4 years; range, 22-100 years). Additional description of the cohort has been published previously.[17]

For the recurrence study, the 1669 incident HZ cases were followed forward for a mean of 7.3 years (range, 1 day to 11.7 years) through December 31, 2007, looking for HZ recurrences. A total of 105 HZ recurrences were confirmed from the medical records of 95 patients, including 6 patients with 2 recurrences, and 2 patients with 3 recurrences. The timing of the first HZ recurrences varied from 96 days to 10 years after the index episode. In 45.0% of the recurrences, the site of the recurrence was in a different region of the body than the site of the index episode.

Table 1 shows the Kaplan-Meier estimated recurrence rates at 2, 4, 6, and 8 years after the index HZ episode overall and by various characteristics at the index HZ episode. The overall Kaplan-Meier estimated recurrence rates at 8 years were 6.2% (95% confidence interval [CI], 4.9%-7.4%) overall, 7.2% (95% CI, 5.4%-9.0%) for wom-

TABLE 1. **Kaplan-Meier Estimates of Overall Recurrence Rates, by Sex and by Characteristics of Initial HZ Episode**

| | No. of | | | Recurrence rate after initial HZ episode, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| | Recurrences | Participants | Person-years | 2 y | 4 y | 6 y | 8 y |
| Overall | 95 | 1669 | 12,143 | 2.0 (1.3-2.7) | 3.6 (2.6-4.5) | 4.9 (3.8-5.9) | 6.2 (4.9-7.4) |
| Sex | | | | | | | |
| Female | 67 | 1005 | 7308 | 2.0 (1.1-2.8) | 3.9 (2.7-5.1) | 5.5 (4.0-7.0) | 7.2 (5.4-9.0) |
| Male | 28 | 664 | 4835 | 2.0 (0.9-3.1) | 3.0 (1.7-4.3) | 3.9 (2.3-5.4) | 4.5 (2.8-6.2) |
| Immune status | | | | | | | |
| Normal | 80 | 1530 | 11,256 | 1.7 (1.0-2.3) | 3.2 (2.3-4.2) | 4.4 (3.3-5.4) | 5.7 (4.4-6.9) |
| Compromised | 15 | 139 | 887 | 5.4 (1.4-9.2) | 7.1 (2.5-11.4) | 10.7 (5.0-16.1) | 12.0 (5.8-17.7) |
| Pain | | | | | | | |
| <30 d | 61 | 1367 | 10,144 | 1.1 (0.6-1.7) | 2.2 (1.4-3.0) | 3.4 (2.4-4.4) | 4.9 (3.6-6.1) |
| ≥30 d | 34 | 302 | 1999 | 5.9 (3.1-8.6) | 9.9 (6.4-13.4) | 11.6 (7.7-15.3) | 12.1 (8.1-15.9) |

CI = confidence interval; HZ = herpes zoster.

en, and 4.5% (95% CI, 2.8%-6.2%) for men. Recurrences were more common among women than among men: 67 (6.7%) of 1005 women had at least 1 recurrence, as compared with 28 (4.2%) of 664 men (*P*=.03; Figure 1).

Kaplan-Meier estimates of recurrence rates by sex and age at the index HZ episode are presented in Table 2. Although one might expect the rates to increase with age, neither a sex effect nor an age trend is statistically significant in Cox regression (*P*=.11 for sex; *P*=.65 for age). Even when restricted to men only, the trend due to age is not significant (*P*=.28) when modeled jointly with other factors. However, both age (*P*=.03) and sex (*P*=.04) are univariately significant.

Only 15 (15.8%) of the 95 persons with recurrences were among the 139 reported to be immunocompromised in the initial incidence cohort (8.3% of the index cohort). The Kaplan-Meier estimate of recurrence rate at 8 years among the immunocompromised group was 12.0% (95% CI, 5.8%-17.7%), as compared with 5.7% (95% CI, 4.4%-6.9%) among those who were immunocompetent at the time of the index episode (Figure 2). However, 90 (85.7%) of 105 recurrences were in those who were initially determined to be immunocompetent.

Described as a continuous variable, the duration of zoster-associated pain in days after the index HZ episode was significantly associated with the likelihood of recurrence (hazard ratio, 2.8; 95% CI, 1.8-4.3; Figure 3). When zoster-associated pain was stratified into periods of less than 30 days, 30 or more days, and 90 or more days, pain of 30 days or longer was the single most predictive factor of recurrence considering immune status, age, sex, pain, and nonpain complications during the index episode. In joint Cox regression modeling, age greater than 50 years and pain of 30 days or longer showed a strong interaction effect (*P*<.001), with a much greater increase in risk of recurrence due to long-duration pain in younger people. The hazard rate for pain duration failed the test for proportionality, with the Kaplan-Meier curve "flattening out" over time. This suggests that persons with pain continuing for at least 30 days after HZ have an increased risk of recurrence in the first 3 to 4 years after the initial episode, but that the predictive effect of pain duration weakens after that.

On the basis of our previous incidence rates,[17] we would have expected 81 incident HZ episodes among a cohort of patients matched by age, sex, and immune status to our original cohort of 1669 index cases. The 81 persons expected to have a first HZ occurrence in this calculation are 15.0% fewer than the 95 persons we identified who had an HZ recurrence (*P*=.29).

In 9 cases, the medical record did not note the side of occurrence. In the 86 persons in whom it was recorded, 38 (44.2%) of the recurrences were contralateral (*P*=.33) to the initial HZ. In the 10 persons with a second or third recurrence, all recurrences were on the same side as the initial recurrence (*P*=.008).

Among the 105 recurrent cases of HZ, 26 (24.8%) were confirmed by laboratory analysis: 12 by viral culture and 14 by polymerase chain reaction.

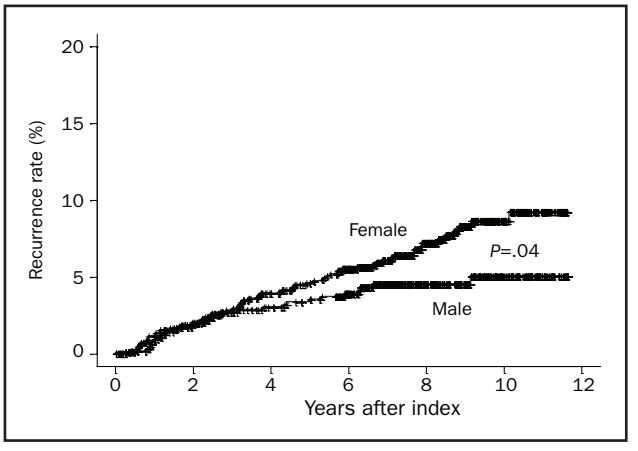


FIGURE 1. Incidence of herpes zoster recurrence since index episode, by sex.

TABLE 2. **Kaplan-Meier Estimates of Age- and Sex-Specific Recurrence**[a,b]

| | No. of | | | Recurrence rate after HZ event, % (95% CI) | | |
|---|---|---|---|---|---|---|
| | Recurrences | Participants | Person-years | 2 y | 4 y | 6 y |
| Males | | | | | | |
| <50 y | 7 | 214 | 1721 | 1.4 (0-3.0) | 2.4 (0.3-4.4) | 3.3 (0.9-5.7) |
| 50-69 y | 10 | 259 | 1996 | 1.6 (0-3.1) | 2.4 (0.5-4.3) | 3.2 (1.0-5.4) |
| ≥70 y | 11 | 191 | 1118 | 3.4 (0.7-6.1) | 4.7 (1.5-7.8) | 5.5 (1.9-9.0) |
| Females | | | | | | |
| <50 y | 17 | 324 | 2650 | 1.9 (0.4-3.3) | 3.1 (1.2-5.0) | 4.3 (2.1-6.5) |
| 50-69 y | 32 | 339 | 2565 | 3.3 (1.4-5.2) | 5.7 (3.2-8.2) | 7.6 (4.7-10.4) |
| ≥70 y | 18 | 342 | 2093 | 0.7 (0-1.6) | 2.9 (0.9-4.9) | 4.6 (2.0-7.2) |

[a] CI = confidence interval; HZ = herpes zoster.
[b] Age stratum determined on the basis of the age at the initial HZ episode.

## DISCUSSION

In a cohort of adults in Olmsted County, Minnesota, with an initial HZ episode from January 1, 1996, through December 31, 2001, the population-based recurrence rate of HZ was 6.2% after 8 years of follow-up. For many people, HZ is not a once-in-a-lifetime event, demonstrating that having HZ does not ensure protection against future HZ episodes. Indeed, after adjustment for age and sex, the rate of recurrent episodes was similar to the incidence rate of HZ episodes in the same population,[17] suggesting that the risk of having another episode of HZ in people with a history of HZ is about the same as the risk of having a first HZ episode in the general population. Laboratory confirmation in 24.8% of cases helps confirm that the recurrences were indeed HZ. Our findings may have implications for HZ recurrence prevention by zoster vaccination.

As anticipated, recurrences were more common among people who were immunocompromised at the time of the index HZ episode, but most recurrences were in people who were immunocompetent at the time of the initial episode. It is possible that some of the people with recurrences may have become immunocompromised between the time of the initial episode and the first recurrence, a possibility that deserves further evaluation in future studies. Zoster-associated pain lasting for 30 or more days at the index episode was a strong predictor of recurrence. Longer-lasting zoster-related pain has been shown to be associated with greater severity of the initial HZ rash and intensity of pain.[16,26] Recurrence could be more common in people with more severe initial HZ, making longer-lasting pain only a proxy measure in our analysis. The medical record data did not provide sufficient detail to assess initial HZ severity so that a definitive answer is not possible from this study. It is also possible that people with milder initial episodes of HZ chose not to seek medical care for any recurrence, leading to underestimation of the number of recurrences.

Our recurrence rates of 5.7% for immunocompetent people and 6.2% overall after 8 years are higher than many of the rates published in the literature. In 1980, Epstein[10] reported that, of 400 persons with HZ, 5 (1.3%) had an HZ recurrence over an unspecified period of time. In the clas-

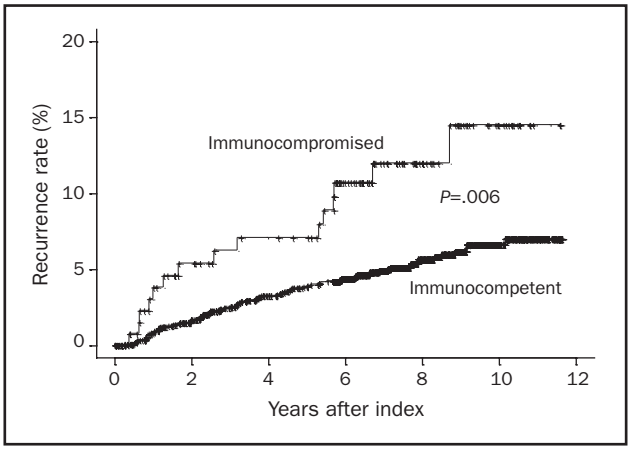


FIGURE 2. Incidence of herpes zoster recurrence since index episode, by immune status at index episode.

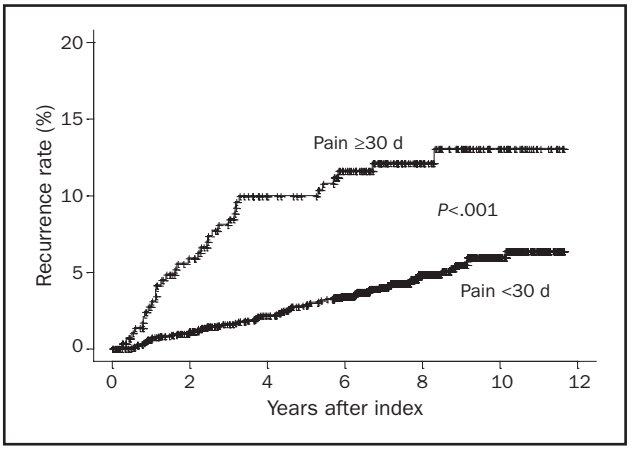


FIGURE 3. Incidence of herpes zoster recurrence since index episode, by pain duration at index episode.

sic paper by Hope-Simpson,[11] 192 HZ cases were identified during 16 years, of which 8 (4.2%) had a second episode and 1 (0.5%) had a third episode. In the same population as our study but during an earlier time period (1945-1959), Ragozzino et al[12] identified 590 persons with a first episode of HZ during the study period, including 31 (5.3%) with a recurrent episode. In 1995, Donahue et al[13] used 2 years of insurance claims data follow-up to identify 4 confirmed and 4 possible recurrences among 1075 patients with an initial episode of HZ. Recurrence rates in the insured population studied were reported as 1.5% during a 2-year period when the "possible" cases were included. This claims database study had no confirmation of diagnosis and a very short follow-up period. In an Icelandic study, 457 patients with HZ were noted to have 4 recurrences (0.9%) during a 5-year study period.[15] An additional 19 (4.7%) of 403 patients for whom retrospective data were available reported a history of typical HZ before the study period. In a retrospective survey of 1071 persons of advanced age, 235 (21.9%) self-reported having had HZ, including 32 (13.6%) of 235 with at least 1 self-reported recurrence.[14] The Shingles Prevention Study, a large clinical trial of the efficacy and safety of a zoster vaccine, was not designed to study recurrence but did report 3 laboratory-confirmed HZ recurrences in 3 years of follow-up among 1308 cases of HZ in immunocompetent people.[16]

Overall, published data on HZ recurrences are scarce and often based on anecdotal reports of small numbers of cases collected using different methods over varying durations of follow-up. Studies that include only 1 to 2 years of follow-up may underestimate the average yearly recurrence rates over a lifetime. A reliable estimate of HZ recurrence requires several years of follow-up. In our study, few recurrences occurred in the first 12 to 18 months after the index case, except in those who were immunocompromised. Our 2-year recurrence rate (2.0%) is similar to that reported by Donahue et al[13] but is poorly predictive of the 8-year recurrence rate.

Unlike other studies, our cohort came from a community-based population with a well-established infrastructure to report administrative diagnoses and allow access to medical records for in-depth review. The ability to obtain follow-up information across all health care facilities within the county is likely to have ensured a high degree of completeness of recurrence identification. Twenty-six (<25%; 9 of them immunocompromised) of our cases had laboratory confirmation of their HZ. This is higher than was anticipated and may be reflective of physicians' desire to confirm that HZ recurrences occur within months to years of the initial HZ episode. The use of a standardized HZ definition requiring both a dermatomal vesicular rash and pain or dysesthesia to confirm the diagnosis of HZ was important for optimizing the specificity of the HZ diagnosis for both the initial and recurrent HZ episodes, with laboratory confirmation a bonus. The specificity of a clinical diagnosis has been confirmed in studies that range from the small (111 patients [specificity 87%][18]) to the very large (>38,000 patients [specificity of 94.0% for the "suspected" cases and >99.0% for the "clinically definite" cases]).[19]

By collecting data on recurrences in both immunocompetent and immunocompromised people, we were able to assess the role played by immune status in the risk of HZ recurrence. Our study did not include assessment of the immune status at the time of the recurrence, a factor that should be assessed in future studies. Although the Kaplan-Meier curves clearly demonstrate the higher rates of recurrence among immunocompromised people (about 2.4 times higher), the overall numbers show that most episodes of recurrent HZ occur in immunocompetent people (85.7%, 90/105). Thus, more than 85% of recurrent cases occur in those eligible to receive a live virus vaccine, such as the currently available zoster vaccine.

If the concept of boosting by exposure to the varicella zoster virus is true, the initial reactivation or HZ episode would be expected to boost immunity and delay a recurrence, with recurrences becoming increasingly more common during the follow-up period. However, the number of recurrences appeared to flatten out over time rather than increase. This lack of apparent boosting effect appears consistent with the lack of a marked increase in the overall HZ rate after introduction of the varicella vaccine for children in the United States and Canada.[17,27] The childhood vaccine should decrease the boosting effect of exposure of adults to children with chickenpox and potentially result in a marked increase in the temporal trend of HZ cases. This effect has not been confirmed.[17,27] An alternative explanation for our results could be an innate (possibly genetic) predisposition for HZ, which has received some attention in studies of HZ in families.[28] This is an area that clearly requires further study.

Although this study on HZ recurrence is the largest to date, it has some limitations. Diagnosis of HZ for both the index and recurrent episodes was based on clinical data, and only a modest proportion of cases were confirmed by laboratory testing. Such is the current standard of care, with HZ considered a clinical diagnosis and laboratory confirmation only used in unusual, unclear, or confusing cases. As a result, HZ could have been overdiagnosed. Conversely, the recurrence rate could be underestimated because not all people with an HZ recurrence may seek care, such as those with a very mild initial case. Also excluded were all possible recurrences that were only included in the differential diagnosis of unexplained pain. All of these factors likely led to an underestimation of the number of recurrences. Interestingly, when reviewing in detail the medical

records of the 1669 confirmed index HZ cases in the initial incidence cohort, we identified 93 persons who had an HZ episode 2 to 50 years before their index episode, despite the absence of an HZ code in the administrative database. This finding suggests that a proportion of HZ cases who seek medical attention may not be coded as such, which may also underestimate the true incidence and recurrence rates. This study was conducted in Olmsted County, Minnesota, where racial diversity is limited among the adult population. This limited racial diversity prevented assessment of possible racial/ethnic differences in HZ recurrence, information that is currently unavailable in the literature. Health care systems are the largest employers in Olmsted County, Minnesota. As a result, our population may have been more aware of possible HZ and more likely to seek health care for it than the general population. The impact of heightened awareness among people who have already had an episode of HZ is unknown but may have been an advantage in this study, in which it was desirable to identify as many cases as possible. Finally, although longer than in most previous studies, the follow-up for recurrence in this study was only slightly longer than 7 years on average. Our results need to be repeated in a larger study sample with longer-term follow-up.

## CONCLUSION

During an average of 7 years of follow-up, HZ recurrences were as common as HZ incident occurrences in the studied population, when matching for age, sex, and immune status. Zoster vaccine is recommended for prevention of incident cases of HZ. Our high HZ recurrence rates suggest that zoster vaccination should be offered in people who have had an HZ episode to prevent potential recurrences.

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